Variation in Experts' Beliefs about Lung Cancer Growth, Progression, and Prognosis

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Introduction: Little is known about the natural history of malignant solitary pulmonary nodules (SPN). Experts' beliefs may help fill these knowledge gaps and explain variation in clinical practices.

Methods: Using a modified Delphi process, we surveyed a group of lung cancer experts about tumor growth, disease progression, and prognosis in patients with malignant SPN. After completing the first survey, experts were given the opportunity during a second survey to revise their responses in light of their peers' beliefs.

Results: The response rate was 100% (14 of 14) for both surveys. There was consensus that disease progression depends on the tumor growth rate, that survival for patients with untreated lung cancer is approximated by a declining exponential function, and that treatment is delayed by approximately 1 tumor volume doubling time (TVDT) in patients who undergo a period of "watchful waiting." Just over half of experts (8 of 14) agreed that lung cancer progresses in three steps (from local to regional to distant disease), whereas 43% (6 of 14) preferred a 2-step model (from local to systemic disease). Likewise, 64% of experts (9 of 14) believed that malignant nodules grow exponentially, whereas 36% (5 of 14) believed that growth is slower than exponential. Experts' estimates of the risk of disease progression during a period of observation lasting 1 TVDT varied from 1 to 50%. Estimates of 5-year survival for patients in whom diagnosis and treatment were delayed by 1 TVDT varied between 40% and 80%.

Conclusions: There is substantial variability in experts' beliefs about the natural history of untreated, malignant SPN. Different beliefs may be partly responsible for variation in management practices.

Key Words: Lung neoplasms, Coin lesion, pulmonary, Delphi technique, survival, disease progression, tumor growth.

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The solitary pulmonary nodule (SPN) is a common and challenging clinical problem. Although evidence-based guidelines and decision analytic models have been developed to help guide clinical decisions about diagnosis and treatment of patients with SPN, these tools are limited by gaps in our current knowledge about the natural history of lung cancer.[1,2] Little is known about the natural history of untreated, malignant lung nodules. More specifically, we know little about the risk of disease progression during a period of diagnostic delay or planned observation. This limits clinicians' ability to counsel patients about the risks associated with a strategy of "watchful waiting." In the absence of empirical data, experts' beliefs may be useful to clinicians and developers of decision aids by filling some knowledge gaps.

The Delphi method was developed in the 1950s by the RAND Corporation to elicit reliable consensus opinion among a group of experts.[3] The technique has been adapted in numerous ways, but centers around repeated questioning of experts, usually in the form of a survey or individual interviews, with feedback on peer responses or thought processes provided between rounds of questioning. The method aims to promote individual thinking by avoiding confrontation between experts, while guiding opinion towards a consensus. The Delphi method has been used to elicit expert consensus about a wide variety of medical topics,[4,5] including management of spontaneous pneumothorax.[6]

In this study, we employed a modified Delphi technique to evaluate expert agreement with assumptions about the natural history of lung cancer, and to measure experts' beliefs about tumor growth, disease progression, and survival in patients with a malignant SPN.

METHODS

We invited leaders from the Thoracic Oncology Network of the American College of Chest Physicians to participate in an expert panel. Follow-up emails were sent to experts who did not respond to the initial invitation. This study was approved by the Institutional Review Board of Stanford University. All participants provided informed consent.

Survey

We measured experts' beliefs about malignant SPN through two rounds of an on-line survey (Appendix). In the first round, we asked experts to provide estimates of median tumor volume doubling times (TVDT), rates of progression from resectable to unresectable disease, and 5-year survival for hypothetical patients with malignant nodules. We also

asked experts to indicate their level of agreement with assumptions about tumor growth rates, disease progression, and survival by using a 5-point Likert scale. We developed survey items based on assumptions from a natural history model of lung cancer.[7,8] We emphasize that the survey was designed to measure beliefs, not to test knowledge.

In the second round of the survey, we again asked experts to indicate their agreement with the assumptions, this time while considering their peers' responses from the previous round. Adjacent to each item, we embedded a bar chart depicting the distribution of first-round responses and an arrow indicating where the participant's previous response fell within that distribution (Appendix). To maintain confidentiality, each participant was sent a unique round 2 survey with only his or her own responses indicated. Participants could keep their responses the same, or revise them in light of their peers' responses.

We also asked multiple choice-type questions about several assumptions in the second round survey. We asked experts to choose between several models of tumor growth (constant, increasing, or decreasing rate), disease progression (3-step, from local to regional to distant, or 2-step, from local to systemic), and survival (quadratic, linear, or exponential curves). We also asked experts to estimate the approximate tumor diameter at which death would occur, on average, in a sample of patients with untreated non-small cell lung cancer (NSCLC).

Statistical Analyses

For Likert scale items, we report the number of experts who agreed or disagreed with each assumption. For estimates, we report range and median values. When we asked experts to estimate values under two different conditions, we calculated the difference between each expert's estimates. We report ranges and median values of these differences. We report detailed results from the second and final survey round only, unless otherwise noted.

RESULTS

The response rate was 100% (14 of 14) in both rounds of the survey. The panel included 9 specialists in pulmonary medicine, 4 thoracic surgeons, and 1 pathologist.

Tumor Growth

There was limited consensus among the experts regarding growth of malignant nodules. In the first survey round, a clear majority of experts (12 of 14) agreed that a 1-cm nodule has doubled in volume 30 times, an assumption consistent with exponential growth. When asked explicitly whether they believed that tumor growth was exponential, 62% (8 of 13) favored this model (Figure 1). When asked to select the tumor growth model with which they most agreed, a majority (9 of 14) chose exponential growth (corresponding to doubling in volume at a constant rate), but a sizable minority (5 of 14) believed that the rate of growth decreased over time.

Disease Progression

There was clear consensus that the probability of disease progression depends on the tumor growth rate, but none of the experts agreed that the monthly probability of progression from local to regional disease equals that for progression from regional to distant disease (Figure 1). Experts appeared to favor a 3-step model of disease progression, with which 9 of 14 agreed. When forced to choose between the 3-step and 2-step models, a slim majority (8 of 14) selected the 3-step model as the most appropriate, whereas a sizable minority (6 of 14) selected the 2-step model. In subsequent discussions with several panel members, they suggested that lung cancer progression may be a 2-step or 3-step process in different patients.

There was clear consensus that treatment is delayed by approximately 1 TVDT in patients who undergo a period of observation, or "watchful waiting," during their evaluation for lung cancer (Figure 1). However, opinion varied widely as to the consequences of such a delay. Experts' estimates of the probability of progressing from resectable to unresectable disease during a delay lasting 1 TVDT ranged from 1 to 50% (Table 1).

Survival

There was consensus that in a sample of patients with potentially resectable NSCLC, survival is approximated by a simple declining exponential function (Figure 1). Four experts reported that survival was best approximated by a quadratic function, and none chose a linear function to de-

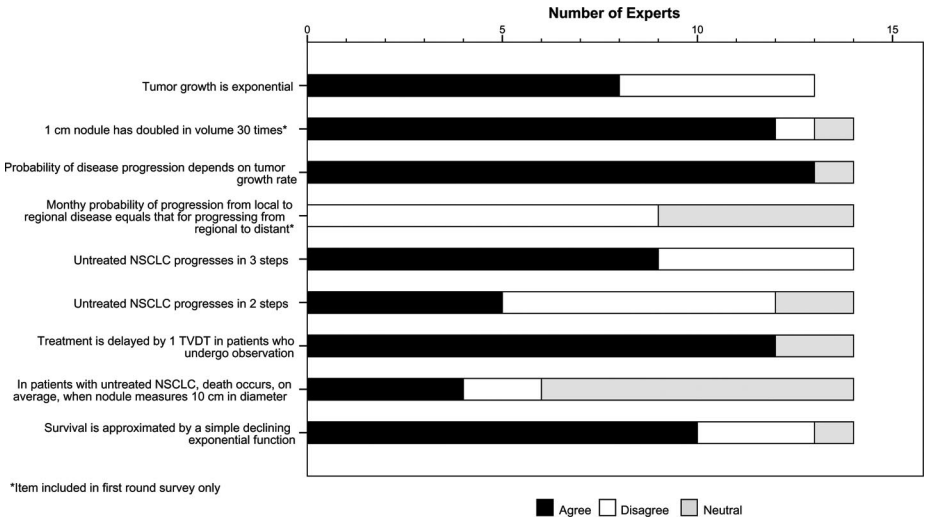

FIGURE 1. Expert Panel Agreement with Assumptions, Round 2. Expert agreement with assumptions about tumor growth, disease progression and survival in patients with NSCLC, after the second survey round. Responses of "Agree" and "Strongly Agree" were combined, as were responses of "Disagree" and "Strongly Disagree." One expert did not provide a response to the final assumption. NSCLC, non-small cell lung cancer; TVDT, tumor volume doubling time.

TABLE 1. Expert Beliefs About Estimates of Tumor Growth, Disease Progression, and Survival

Estimate	*n*	Median	Range
Median tumor doubling time (mo)[a]	14	4	1.5–14
Probability of progression from resectable to unresectable disease during delay of 1 TVDT[b]	14	10%	1–50%
Average diameter (cm) of primary tumor at time of death[c]	13	5	1–10
Probability of 5-yr survival if nodule resected without delay[b]	14	70%	60–80%
Probability of 5-yr survival if resection delayed by 1 TVDT[b]	14	65%	40–80%

[a] For clinically-detected 1.6 cm NSCLC.

[b] For a 62-yr-old asymptomatic man with a 1.6 cm malignant solitary pulmonary nodule due to NSCLC. No evidence of hilar or mediastinal lymph node enlargement on chest CT.

[c] For a sample of patients with untreated NSCLC.

TVDT, tumor volume doubling time; NSCLC, non-small cell lung cancer; CT, computed tomography.

scribe survival. Estimates of the probability of 5-year survival with and without prompt treatment varied widely (Table 1). The median difference between estimates of 5-year survival with and without delayed treatment was 5% (range, 0–20%).

In an untreated patient with NSCLC, the median tumor diameter at the time of death was believed to be 5 cm (range, 1–10 cm) (Table 1). Only four participants believed that the average tumor diameter at the time of death was 10 cm (Figure 1).

In general, responses changed only slightly from round 1 to round 2. In 4 of 7 questions that were asked in both rounds, the median response (weak agreement) did not change, but a small number of panelists modified their response by moving closer to the median value. In one item (death after 40 doublings in volume), 4 respondents moved closer to the median response (neutral) and 1 moved away. In another item (lung cancer progresses in 2 steps), 3 respondents moved away from the median response (neutral) and 4 actually reversed their positions (2 from agreement to disagreement and 2 from disagreement to agreement). In one item (exponential growth), the median value changed from neutral to weak agreement after 3 participants modified their responses.

DISCUSSION

These results offer a first look at experts' beliefs about the natural history of malignant SPN. Although some consensus existed among this small panel of experts, we observed substantial variability in their beliefs. This variability is likely explained in part by gaps in our current knowledge about tumor biology and the natural history of lung cancer.

One simple model of natural history assumes that a tumor begins as a single cell that measures 10 μm in diameter and grows exponentially (i.e., it doubles in volume at a constant rate), and that on average, in the absence of treatment, death occurs after 40 doublings in tumor volume, at which time the tumor measures 10 cm in diameter.[7,8] Our results suggest that the face validity of this model is limited.

Our most striking finding is the variability in experts' estimates of the risk of disease progression during a period of observation lasting 1 TVDT, which ranged from 1 to 50%. Estimates of 5-year survival for patients in whom diagnosis and treatment were delayed also varied greatly (range, 40–80%). Other areas of important disagreement include beliefs about growth rates (exponential versus slower than exponential) and disease progression (3-steps versus 2-steps).

This study is limited by its small sample size, and the results may not be generalizable to other groups of experts or practicing clinicians. In most cases, we measured beliefs by using a single item, and while items were not formally validated, we believe that face validity was excellent.

In the absence of empirical data, beliefs about tumor growth and disease progression may play a role in guiding decisions about patient care. For example, clinicians who believe that malignant nodules are likely to progress from resectable to unresectable disease if diagnosis is delayed may be more likely to refer for prompt surgical resection, rather than performing a biopsy or recommending follow-up with serial imaging tests. Further research is needed to test this hypothesis and to explore the relationship between physicians' beliefs and practices. In particular, future work should examine beliefs about tumor growth, disease progression, and survival in a sample of practicing clinicians. In addition, this work should be coupled with ongoing bench and translational research into the biology of tumor growth and promoters of tumor spread.

In conclusion, this study represents the first survey, to our knowledge, of experts' beliefs about lung cancer growth, progression, and prognosis. Our results show that experts hold different beliefs about the natural history of lung cancer and suggest the possibility that these differences may partially explain variation in practices for managing patients with SPN.

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APPENDIX

First Round Survey—Page 1

We would like to know your opinions and beliefs regarding tumor growth, disease progression and prognosis in patients with lung cancer. Please provide your best estimate for each question. When you are satisfied with your entries, please click "Submit" to record your responses and continue with the survey.

1) What is the median tumor doubling time (measured in months) for a clinically detected non-small cell lung cancer measuring 1.6 cm in diameter? Remember that one doubling in tumor volume corresponds to a 26% increase in tumor diameter. ____ months

When answering questions #2 through #4, please assume that the patient is a 62-year old man with a malignant solitary pulmonary nodule due to non-small cell lung cancer that measures 1.6 cm in diameter. The patient is asymptomatic and there is no evidence of hilar or mediastinal lymph node enlargement on chest computed tomography.

2) In this patient, what is the probability of 5-year survival if the nodule is resected without delay? ____ %

3) In this patient, what is the probability of 5-year survival if resection is delayed by one tumor volume doubling time? ____ %

4) In this patient, what is the probability of progression from resectable to unresectable disease during a period of observation lasting one tumor volume doubling time? ____ %

When answering questions #5 and #6, please assume that the patient is a 62-year old man with a non-small cell lung cancer and a T2 primary tumor that measures 3.8 cm in diameter. A thorough clinical evaluation (history, physical, chest x-ray and routine laboratory studies) reveals no evidence of metastatic disease and there is no medical contraindication to surgical treatment.

5) In this patient, what is the probability of 5-year survival if the patient is treated with thoracotomy and lobectomy? Assume that no evidence of hilar, mediastinal or other metastasis is found at the time of resection. ____ %

6) In this patient, what is the probability of 5-year survival if the patient has a false positive staging evaluation and is treated with combined chemotherapy and radiation rather than surgery? ____ %

First Round Survey—Page 2

We would like to know how you feel about each of the following statements. Please indicate your level of agreement or disagreement by selecting one of the options to the right. You may select only one option for each statement. To change your selection, simply click on a different option. When you are satisfied with your selections, please click "Submit" to record your responses and continue with the survey.

Assumptions	Strongly Agree	Agree	Neutral	Disagree	Strongly Disagree
A tumor doubles in volume at a constant rate, i.e. tumor growth is exponential.	○	○	○	○	○
An assumption of exponential growth implies that a tumor that measures 1 cm in diameter has doubled in volume approximately 30 times.	○	○	○	○	○
In patients with lung cancer, death occurs, on average, after 40 tumor volume doubling times, when the primary tumor diameter measures approximately 10 cm.	○	○	○	○	○
In most cases, untreated non-small cell lung cancer progresses sequentially in 3 steps, from local to regional to distant disease, and then to death.	○	○	○	○	○
In most cases, untreated non-small cell lung cancer progresses sequentially in 2 steps, from local to systemic disease, and then to death.	○	○	○	○	○
The probability of progression from local to more advanced lung cancer is proportional to the growth rate of the tumor.	○	○	○	○	○

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